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Article (Accepted Version)

Comprehensive Geriatric Assessment in Men Aged 70 Years or Older with Localised Prostate Cancer Undergoing Radical Radiotherapy

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Abstract

Aims

Treatment decisions for men aged 70 years or over with localised prostate cancer need to take into account the risk of death from competing causes and fitness for the proposed treatment. Objective assessments such as those included in a comprehensive geriatric assessment (CGA) might help to inform the decision-making process. The aim of this study was to describe the CGA scores of a cohort of older men with prostate cancer, evaluate potential screening tools in this population and assess whether any CGA component predicts significant acute radiotherapy toxicity.

Materials and methods

This was a prospective cohort study undertaking pretreatment CGA, Vulnerable Elders Survey (VES-13) and G8 assessment in patients aged 70 years and over with localised prostate cancer planned to undergo radical external beam radiotherapy.

Results

In total, 178 participants were recruited over a 3 year period and underwent a CGA. Fifty-five (30.1%) participants were defined as having health needs identified by their CGA. Both VES-13 and G8 screening tools showed a statistically significant association with CGA needs ($P < 0.001$ and $X2 = 15.02$, $P < 0.001$, respectively), but their sensitivity was disappointing. There was no association between a CGA (or its components) and significant acute radiotherapy toxicity.

Conclusions

Many older men with localised prostate cancer are vulnerable according to a CGA. The screening tools evaluated were not sufficiently sensitive to identify this group. CGA outcome does not predict for significant acute radiotherapy toxicity.

Key words: Comprehensive geriatric assessment; elderly; geriatric oncology; prostate cancer; radiotherapy tolerance; screening tests; toxicity

Background

Over the last thirty years, there has been a four-fold increase in the incidence of prostate cancer (PC) in men aged 70 or over in England [1]. In 2010, the National Cancer Equality Initiative described inequalities in cancer care in the UK and identified that older people with cancer receive less intensive treatment than younger people [2]. In some scenarios this may be clinically appropriate [3,4] but when patient chronological age alone determines extent of intervention, there is the potential for significant under-treatment to occur [5,6,7]. There is considerable scope for both under- and over-treatment in the management of localised PC, where treatment options include radical surgery or radiotherapy; primary endocrine therapy or active surveillance. The decision as to which treatment approach is most appropriate for an individual patient depends on tumour characteristics, the risk of death from competing causes, fitness for the proposed treatment and patient wishes. As the population ages and a greater number of older patients are diagnosed with PC [8,9], such decisions will increasingly be faced.

It has been proposed that a global assessment of health termed a Comprehensive Geriatric Assessment (CGA) may be a useful objective measure by which to define health and predict risk of death from competing causes of mortality and toxicity from treatment in older patients with cancer [10]. A CGA assesses functional ability, co-morbidities and nutritional, cognitive, psychological and social status by means of a number of questionnaires. Many versions are available in the literature [11,12] and several studies have demonstrated their use in identifying vulnerable older cancer patients [13,14]. CGA may consequently have a role in predicting impaired tolerance and completion of oncological treatment, increased toxicity and need for treatment modification in this setting [15].

Once a CGA assessment is made, this result should be used as a trigger for further assessment and optimization of the patient to address any reversible causes. A variety of models could be employed including, but not limited to, referral to a specialist geriatric service. There is limited evidence within the cancer population regarding the impact of a CGA, subsequent intervention on treatment received or cancer outcomes [15]. In localised PC, where radical radiotherapy

typically commences after an induction period of androgen deprivation therapy, there is time to allow optimization of patients before making a final decision on whether a patient is suitable for radical radiotherapy. However, prognostic validation studies in patients with early prostate cancer are lacking and studies predicting tolerance of treatment are limited.

The time constraints and staff competencies of standard oncological practice make full CGA challenging outside of a research setting but a screening tool could be done as part of a holistic needs assessment; this could be a workable solution particularly if performed by a specialist nurse or support worker, enabling geriatric assessment for all patients. A number of screening tools are available [16] and we have evaluated two in this population. The VES-13 is a 13 item questionnaire covering age, self-rated health, limitations in physical function and functional disabilities. In the general geriatric population (aged 65 or over), those with a score of ≥ 3 have a 4.2 times increased risk of death or functional decline over a two-year period compared with those with scores <3 (49.8 vs 11.8%) [17]. The G8 screening tool was developed for use in the cancer population and so there is no data available for its use in the general population. The G8 covers nutritional intake, BMI, mobility, neuropsychological problems, number of medications, and self-rated health [18]. A score of ≤ 14 has been shown to predict functional decline, chemotherapy related toxicity and survival in several studies in solid tumours [16]. The G8 screening tool was included in the EORTC "minimum dataset" for CGA in patients with cancer in 2011 [19].

In this study, we describe the distribution of CGA scores in a population of men aged 70 or over with a diagnosis of localised (non-metastatic) PC who are undergoing radical radiotherapy. Our aims were to describe the proportion of patients in whom a CGA identifies significant health needs, to identify if short screening tools may be an alternative to a comprehensive assessment in all patients and to examine if CGA scores predict significant acute radiotherapy toxicity. Further follow-up of this cohort will examine the role of CGA and screening tools in predicting functional decline in the years immediately following treatment and therefore assess whether they are useful in determining which patients (who appear fit on standard clinical review) might not derive benefit from radical treatment due to competing co-morbidities.

Materials and Methods

Study Design. Prospective cohort study.

Participants. Inclusion criteria were men aged ≥ 70 years, diagnosed with histologically proven PC of any T stage and Gleason score with N0 M0 disease. All participants were planned to receive fractionated external beam radiotherapy with radical intent, with endocrine treatment of any duration permissible. Exclusion criteria were inability to give informed consent, a life expectancy less than three months, prior commencement or receipt of radical radiotherapy or prostatectomy (noting that a previous TURP was permissible).

Setting. Study recruitment occurred from December 2011 to December 2014, in outpatient departments at three hospital trusts in the Sussex Cancer Network, UK. All participants gave written informed consent for participation. The study was approved by NRES South East Coast-Surrey (11/LO/1382) and R&D approval provided by participating trusts.

Data Collection. Baseline assessments were taken within two months prior to commencement of radiotherapy. Patient demographics, Charlson co-morbidity index [20,21,22], body mass index (BMI), medications, tumour characteristics and treatment details were extracted from medical records. The following data were attained through a structured questionnaire via patient interview (by telephone or in person): WHO Performance Status (PS) (0-4), Vulnerable Elders Survey (VES-13) (0-13) [17,23], G8 score (0-17) [18,24], Activities of Daily Living (ADL) (0-6) [10], Independent Activities of Daily Living (IADL) (0-8) [25], mini nutritional assessment (MNA) (0-14) [26], social network index (SNI) (1-4) [27], place of residence and falls in the preceding six months.

Follow up data were recorded at twelve weeks post completion of radiotherapy. Radiotherapy treatment was detailed to include dose, schedule, and start dates. 30 day mortality was checked prior to patient phone call. Acute bowel and genitourinary side-effects (Radiation Therapy Oncology Group (RTOG) graded from 0-5 [28] and treatment-related medical contacts

(including GP attendance and inpatient admission) were recorded from patient telephone interview.

The primary toxicity outcome was significant acute radiotherapy toxicity, defined as RTOG Grade 2-5 genitourinary/bowel side-effects or acute hospital admission related to treatment, at any point in the twelve weeks following radiotherapy. Traditionally severe toxicity is defined as RTOG grade 3-5; however, grade 2 toxicity (defined as having an impact on iADLS such as meal preparation and simple tasks such as shopping) would constitute "significant" toxicity in an older population where independent functioning may be more vulnerable. This is in line with the recently published CHHiP trial which chose a threshold of > 2 when describing the toxicity experienced in a population of men receiving radical radiotherapy for PC of all ages, with a median age of 69 years [29].

Data Analysis. Data were analysed using the statistical package IBM SPSS Statistics. The distributions of the following CGA components were handled continuously: age, WHO PS, ADL, IADL, Charlson comorbidity score, medication number, MNA, BMI and SNI. Distributions of certain components were handled recognizing the following cut-offs: place of residence (own-home/warden-controlled/residential-home/nursing-home), cohabitation (lives alone/other), presence of prior falls, cognitive/psychological history (0 vs 1 vs 2), VES-13 (<3 vs $\geq$ 3), G8 ($\leq$14 vs >14) and CGA needs (negative vs positive).

For the purposes of this study, a positive 'CGA needs' result was defined as a deficit in specified functional domains (dependence in I/ADLs (8 vs <8 and 6 vs < 6 respectively), medication number > 9, residence in a nursing or residential home or having fallen within the six months prior to assessment). This pragmatic definition includes information that would be routinely collected during an oncology clinic appointment, yet would raise clinical concern regarding fitness for intensive treatments.

VES-13 scores $\geq$ 3 and G8 scores $\leq$14 were defined as positive results for these screening tests, suggesting the need for a fuller CGA, in line with the published results for these tools [17,18].

A logistic regression model was used with five input variables (age, CGA needs, MNA, PS and Charlson comorbidity score) with the primary outcome being significant acute radiotherapy toxicity. These were selected for their clinical relevance, alongside preference for continuous, normally distributed inputs. Other parameters not included in the composite 'CGA need' measure will further analysed when longer term outcome data is available.

Sensitivity, specificity, positive and negative predictive rates for a positive 'CGA needs' outcome were calculated for the VES-13 and G8 screening tests (alongside Fisher's exact test and two-sided chi-squared tests of association where appropriate). Missing values were accounted for within multivariate analysis and have been declared amongst the baseline results.

Results

One hundred and eighty-one participants were recruited but three were excluded owing to eligibility and inadequate baseline data, leaving 178 remaining participants with data to be analysed for distribution of CGA components.

Patient demographics, tumour characteristics and distribution of CGA components: Participant demographics are shown in **Table 1**. The median age was 74 years old (range 70-84 years). Tumour characteristics are presented in **Table 2**. Median presenting PSA was 12ng/mL (ranging from 3 to 395ng/mL), median duration of hormone treatment prior to radiotherapy was six months and median total planned hormone duration was 22 months. Baseline CGA scores are shown in **Table 3**. One hundred and sixty-eight patients (94.4% of the study population) had sufficiently complete domains ((I)ADL, medication number, residence and falls) to calculate CGA needs. Of these, 55 (30.9%) were defined as having 'CGA needs'. 46 scored on one domain only, five on two domains and four on three domains. Components that identified 'CGA need' were distributed across the domains: 23 due to ADL dependence, 22 to falls, 11 to IADL dependence, 9 to medication number and 3 to residence.

Significant acute radiotherapy toxicity: Radiotherapy toxicity data within twelve weeks post treatment were available for 162 patients (91.0% of the study population). One hundred and twenty eight (79.0%) patients experienced some acute side-effects (RTOG 1-5); 51 (31.5%) experienced significant acute side-effects (RTOG grade 2-5). Four (2.5%) participants experienced a treatment-related inpatient admission and twenty-six (16.0%) visited their GP regarding side effects. 53 (32.7%) participants experienced significant acute radiotherapy toxicity, defined as bladder or bowel toxicity (RTOG grade 2-5) or admission. There were two patients admitted who did not meet specific bladder and bowel toxicity criteria, yet these admissions were felt to be related to the more general effects of radiotherapy, including fatigue and interruption of normal social function which might predispose vulnerable patients to

concurrent illness.

There were no deaths in the cohort at twelve weeks post radiotherapy treatment, and no patients stopped radiotherapy prior to completion. Ninety-six percent of radiotherapy courses were delivered as planned with 56.8% of patients receiving a 74Gy regime and 38.3% receiving a 57Gy regime.

Association of CGA components with significant acute radiotherapy toxicity: There were 133 complete observations in the logistic regression model including 44 cases of significant acute radiotherapy toxicity: this comprised 83% of all the cases of significant acute radiotherapy toxicity recorded. There was no statistically significant association between a positive CGA needs result and significant acute radiotherapy toxicity. Age, Charlson co-morbidity score, PS and MNA also did not predict this primary outcome (**Table 4**).

Sensitivity and specificity of VES-13 and G8 compared to fuller CGA screening: Distribution of scores for VES-13 and G8 scores are shown in **Figure 1**. For cross-tabulation with CGA needs, there were 168 complete observations for VES-13 scores and 156 complete observations for G8 scores (**Table 5 in appendices**). Both VES-13 and G8 scoring were shown to have a statistically significant association with positive CGA needs ((p< 0.0001 using Fisher's Exact test and $X^2 = 15.02$, p <0.0001 using Chi-squared analysis, respectively).

The VES-13 screening tool had 20.0% (11/55) sensitivity, 100% (113/113) specificity, 100% (11/11) positive predictive value and 72.0% (113/157) negative predictive value. The G8 screening tool had 44.7% (21/47) sensitivity, 84.4% (92/109) specificity, 55.3% (21/38) positive predictive value and 78.0% (92/118) negative predictive value.

Discussion

Thirty one percent of older PC patients, already clinically assessed as suitable for radical radiotherapy were shown to be vulnerable according to a multi-domain Comprehensive Geriatric Assessment. The wide distribution of scores amongst individual CGA components further show that the study population is heterogeneous in a range of domains, with impairment most frequently seen amongst ADLs, G8 scoring, medication number and social and cognitive function. While this population appeared "fit" on clinical assessment (with almost 95% being performance status 0-1), significant numbers had deficits in domains that might question the appropriateness of radical treatment, including ADL and IADL dependence, medication number and recent falls. To our knowledge, this is the first study to define a population of older men undergoing radical radiotherapy for localised PC in terms of a CGA, evaluate potential screening tools and describe its correlation with acute radiotherapy outcomes.

The degree of functional impairment demonstrated in this study is comparable to previous limited data in the area. In a French cohort of unselected older PC patients with variable disease stage, including metastatic disease, 66% showed dependence in one or more ADL, 87% were dependent in one of more IADL and 65% were at risk or with malnutrition [30]. Furthermore, 6.7% risk of malnutrition in our study's setting of localised disease is concordant with a recent cross sectional study, where 7.5% of those with benign prostate disease and 50% of those with metastatic PC were at risk of malnutrition [31]. The predominance of no/mild comorbidity shown in an American study of older PC patients with localised disease only, is comparable to 70.2% of our cohort having a Charlson score of one or less [14]. This would suggest that comorbidity alone may not be sensitive enough to highlight potential impaired tolerance to treatment, as supported by recent work studying 185 older patients with colorectal cancer, where co-morbidity had poor predictive value for severe chemotherapy toxicity [32].

Short screening tools are likely to be more readily integrated into routine oncological care. Both the VES-13 and G8 have been extensively studied in variety of cancer (and non-cancer populations) and there is variability in their ability to predict functional decline and cancer

outcomes [16]. As screening tools predicting for a positive score on full CGA assessment, specificity has been variable, although sensitivity has been found to be high [16]. This is not in keeping with our findings, where both tools exhibited high specificity but relatively low sensitivity. This is important, both for their future use in this population, and also as a marker of the potential differences in our population, who had been pre-selected for radical treatment and therefore might be expected to be "fit", or appear to be. It is important to note however that these screening tools hold value over and above their numerical "score" as they identify domains that may require attention.

There was no association between CGA (or its components) and significant acute radiotherapy toxicity. Interestingly however, the toxicity rates in this population were higher than those reported in the CHHiP study; 51% in our study compared to 25 and 38% (depending on dose/fractionation) [29]. This may support the expectation that older patients are at risk of increased toxicity. Furthermore, the high rates of significant acute toxicity shown in our study is clinically relevant and of concern when considering treating older patients with radical radiotherapy. Despite this, the fact that 'CGA needs' did not predict for significant acute radiotherapy toxicity could lend support for the use of radiotherapy in an older population as compared to surgery, where morbidity and mortality rise with age.

The significant health impairment reflected by a positive 'CGA needs' status in our study may instead be a surrogate marker for underlying, competing health issues; in time, these may render increased susceptibility to chronic bowel and bladder dysfunction, or have a greater impact on the patient's future health than their prostate cancer, undermining the role and benefit of upfront radical treatment. Future results from this study will evaluate these outcomes further.

Previous studies in non-cancer and non-PC populations have shown that components of the CGA including VES-13 and G8, can predict risk of death, functional decline and health service use over a two and five year timeframe period [33,34,35]. In a mixed cancer population including patients treated with radical and palliative intent, VES-13 had predictive value for

completion of radiotherapy [36] and in an analogous setting, geriatrician-led intervention based on CGA has been associated with improved chemotherapy tolerance in older cancer patients [15]. A key question which will be addressed in longer term follow up of this cohort will be whether these tests predict functional decline and death (including death from non-cancer causes) in older men with localised PC. If this is the case they may prove to be useful tools by which to triage patients to the different treatment options available. For example, one could propose a model by which those with a high risk of death from competing causes of mortality might be best served by active surveillance or endocrine therapy alone, rather than more radical approaches.

The assessments used to define 'CGA need', which did identify 31% of this population as vulnerable, are not particularly onerous or specialist. The majority should be included in a first consultation with an oncologist, including residence and medication number; whilst much of the domains assessed in both ADLS and IADLS will also be covered. We propose that this level of assessment could in fact form an initial assessment which could be completed by a specialist nurse or trained support worker. In this population, all of these domains appear to be necessary to identify this group of potentially vulnerable patients, as 46/55 patients identified scored on one domain only and the domains on which patients scored were distributed across all those collected. Whether this definition of 'CGA need' predicts for chronic toxicity, functional decline or death remains to be seen.

This population might differ from those included in many studies of CGA and screening tools in a number of ways. Importantly they had been pre-selected for radical treatment; we anticipate that those not clinically deemed suitable for radical treatment were more likely to be identified as vulnerable on both screening tests and a full CGA, and an unselected population might have approximated more closely to the populations in whom these screening tools were developed. It has been noted that the age threshold of this study (70 years) is lower than that sometimes used to define an "older adult" with cancer and that the patients were generally of good performance status and had little comorbidity. However, a third of patients were still vulnerable on a multi-

domain CGA, suggesting that clinical decision-making alone does not replace a more thorough assessment. Performance status alone did not identify this group, or those identified as vulnerable using either screening test. The consequences of being in this "vulnerable" group of this population remain to be seen, with further data collection and analysis of longer term outcomes.

A limitation of this study is that the pre-selected nature of this group renders a potential to identify over -treatment of vulnerable men but not under-treatment of those initially deemed unsuitable for radical radiotherapy. Furthermore there is a risk that studies of this nature recruit better in affluent areas, and vulnerability might be expected to be greater if the study were to be repeated in areas of higher social deprivation. Indeed, identifying the latter on CGA could direct optimization of functional status and in turn, increase treatment options available to them.

In summary, many older men with localised PC, selected for radical radiotherapy, are vulnerable according to a CGA. Brief screening tools (VES-13 and G8) were not sufficiently sensitive in this population to identify those who a multi-domain CGA scored as vulnerable. A CGA did not identify those patients at risk of significant acute radiotherapy toxicity. Longer term follow-up of this cohort will identify whether a CGA predicts risk of functional decline and death from competing causes of mortality and thereby a means by which to select treatment options in older patients with localised prostate cancer.

Acknowledgements

The authors would like to thank the Sussex Cancer Fund for supporting the research, and Dr Ring acknowledges the support of the Royal Marsden National Institute for Health Research Biomedical Research Centre for Cancer. The authors have no conflicts of interests to declare.

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